result in a thermal curve showing only an endothermic melt, like that shown earlier in Figure 23.1. If the sample put into the DSC initially is a metastable form, then an alternate thermal curve is likely, Figure 23.14 (top curve). Here three events are seen; an endotherm followed by an exotherm followed by an endotherm. To what phase transitions can these events be assigned? The low temperature endotherm is easily assigned to melting of the metastable form. At a temperature immediately after the endotherm the sample is thus molten; but because the form that melted was metastable, and so at least one higher melting point form is available, the liquid is *supercooled*. With time, the liquid will crystallize to the next thermodynamically available solid form (in this case the stable polymorph). Crystallization is (usually) exothermic and so accounts for the exotherm on the DSC thermal curve. Finally, the stable form melts; the higher temperature endotherm. This pattern of transitions (endotherm-exotherm-endotherm) is a characteristic indicator of the presence of a metastable polymorph (indeed, if more than one metastable form is available, then an additional endotherm-exotherm sequence will be seen for each one). If the sample is cooled to room temperature and then reheated, often only the melting of the stable form in seen (Fig. 23.14, bottom curve). The combination of XRPD and DSC is very powerful and allows rapid assignment of polymorphic forms.

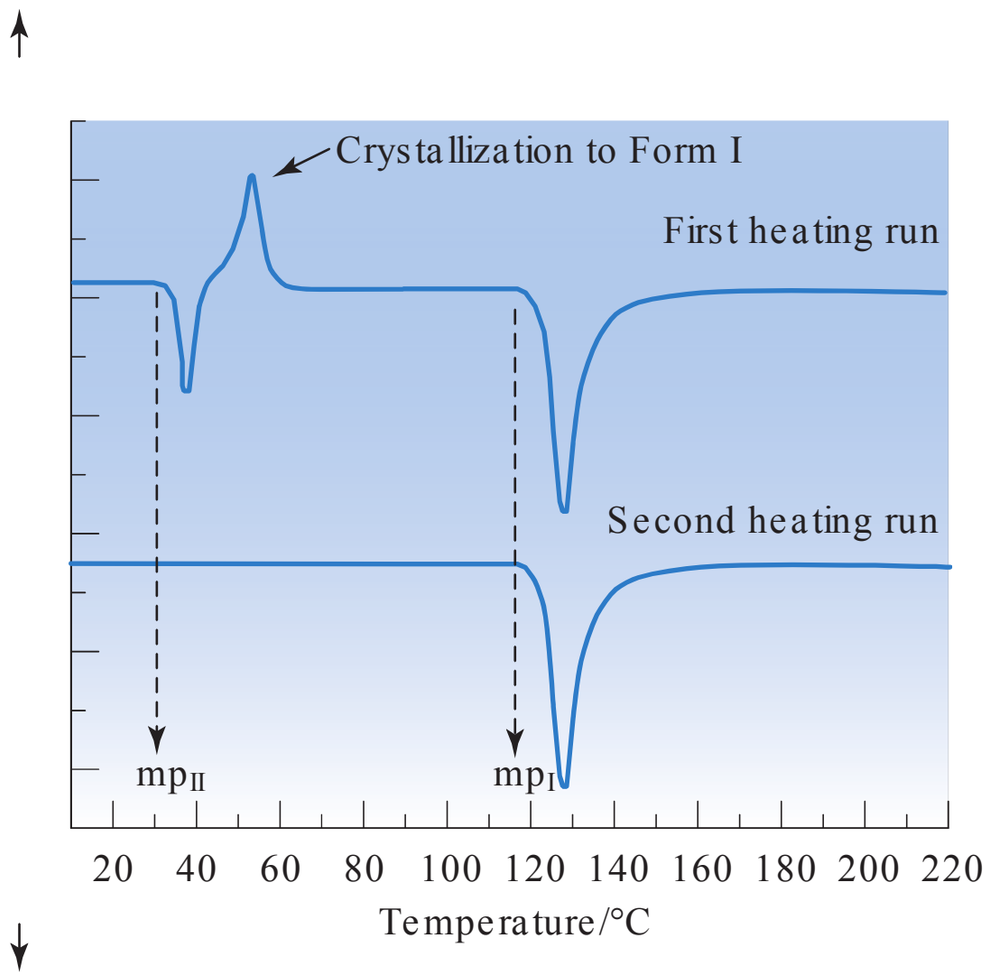

Fig. 23.14 • Schematic representation of the DSC thermal curves for a meta-stable polymorph on its first (top) and second (bottom) heating runs.

Amorphous materials

Several factors can make it difficult for molecules to orient themselves, in large numbers, into repeating arrays. One is if the molecular weight of the compound is very high (for example, if the active is a derivatized polymer or a biological material). Another factor is if the solid phase is formed very rapidly (say by quench-cooling or precipitation), wherein the molecules don't have sufficient time to align. It is also possible to disrupt a pre-existing crystal structure with application of a localized force (for example, by milling). In any of these cases, the solid phase so produced cannot be characterized by a repeating unit cell arrangement and the matrix is termed *amorphous* (see also Chapter 8).

Because amorphous materials have no lattice energy and are essentially unstable (over time they will convert to a crystalline form) they usually have appreciably higher solubilities and faster dissolution rates than their crystalline equivalents, and so offer an alternative to salt selection as a strategy to improve the bioavailability of poorly soluble compounds.

Confirmation that a material is amorphous can be achieved with XRPD. In this case, no specific peaks as a function of diffraction angle should be seen; rather, a broad diffraction pattern, known as a 'halo', is the defining characteristic, as shown in Figure 23.15.

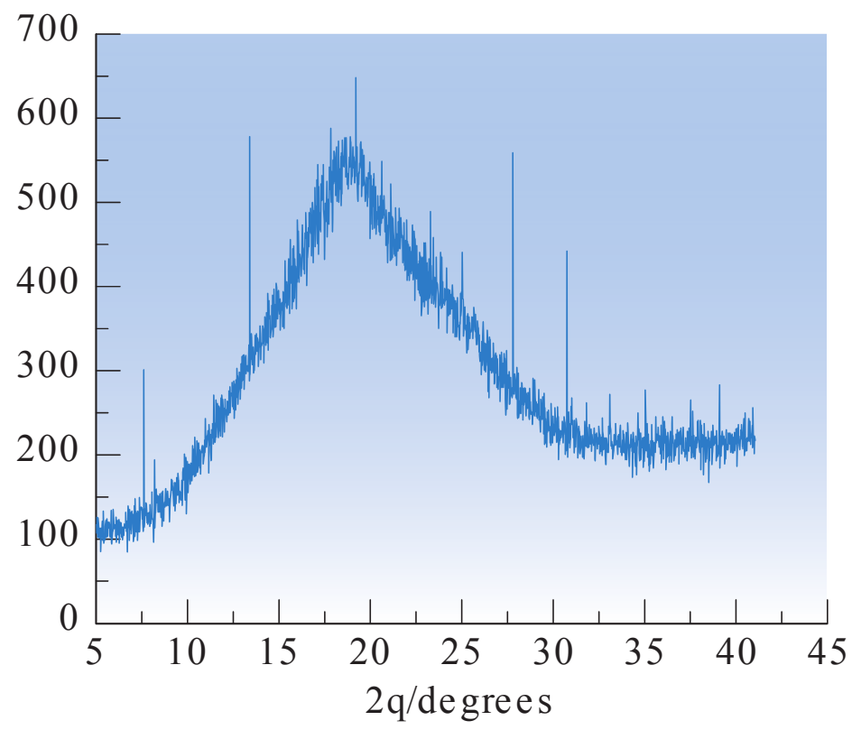

Fig. 23.15 • XRPD diffractogram for amorphous trehalose.